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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,289	03/23/2001	Carl R. Merril	PNC-001	6112

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EXAMINER	
GUCKER, STEPHEN	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,289	MERRIL ET AL.	
	Examiner	Art Unit	
	Stephen Gucker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

R sponse to Am ndment

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/23/06 has been entered.

2. Claims 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record and the following. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant invention is drawn to methods of treatment of the genus of neurodegenerative diseases of mammals in need of such treatment by administering an agent, such as a diphtheria toxoid vaccine composition (i.e. a diphtheria vaccination), in order to inhibit and/or reverse ADP-ribosylation of elongation factor-2 (EF-2) in neurons, thereby ameliorating the neuronal degeneration. However, the disclosure does not provide adequate guidance or sound scientific reasoning to suggest to the skilled artisan that the instant invention is enabled without resorting to unpredictable and unreasonable experimentation in order to place the invention into the hands of the public for the following reasons. It is noted that the specification provides no working examples of the instant invention, so in order to make a determination of whether or not the instant methods are adequately enabled by the

completely prophetic disclosure, an analysis of the working hypothesis underlining the instant invention must be undertaken. If the guidance provided by the teachings of the specification and the prior art are adequate, then the instant invention can be determined to be enabled in the absence of any working examples. Similarly, if the disclosure sets forth sound scientific reasoning to support its prophetic assertions, a determination of enablement can also be achieved in the absence of any working examples.

The specification sets forth the proposition that the genus of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and schizophrenia are likely caused by diphtheria toxin or other ADP-ribosylating toxins that are secreted by pre-existing infections by organisms such as *Corynebacterium diphtheria* in individuals where the body's immune system is no longer capable of effectively neutralizing such toxins due to aging (see specification, page 6, lines 4-19; page 7, lines 3-17; and page 8, line 22 to page 9, line 5). If age-related decline in immune function is the underlying physiological deficit that the instant invention is intended to treat, then the instant invention is not enabled for treating neurodegenerative diseases that are not associated with aging such as schizophrenia (the primary incidence of schizophrenia occurs in young adulthood). Furthermore, the specification teaches that "the ability of the immune system to respond adequately to the diphtheria toxin likely diminishes with age" (page 6, lines 12-15). Therefore, the specification itself provides guidance that the instant invention is not operative, absent evidence to the contrary. The disclosure teaches that the prior art has shown that the military has a lower rate of age-related cognitive decline

compared to the general population (McLay, reference CF on PTO-1449 filed 10/5/01) and Applicant attributes this finding to his belief that the military tends to keep up their immunizations for diphtheria. However, no support for this belief is found in the McLay reference. In fact, McLay is unable to explain his findings satisfactorily and lists as possible explanations the effect of psychological prescreening and screening for military personnel and the educational benefit of early military service (page 624). Another difficulty that the skilled artisan would have in accepting the guidance and scientific reasoning of the prophetic specification is that if a decline in immune function in the elderly is allowing the toxin from *C. diphtheria* to kill neurons, then why doesn't the incidence of the disease diphtheria itself increase with age? There is no evidence that this Examiner was able to find by searching that compared the well-known and dramatic increased incidence of Alzheimer's Disease (AD) with age with a comparable increase of diphtheria in the elderly. Finally, the specification is silent concerning such conditions known as presenile dementia of the Alzheimer's type or early-onset AD, which occurs in younger individuals than "classical" AD. If neurodegenerative diseases such as AD occur due to impaired immune function due to aging, how then does it occur in non-immune impaired younger individuals? All of the foregoing casts serious and significant doubt that the instant invention could be enabled by the skilled artisan with the guidance and reasoning taught by the instant specification by using routine experimentation.

The specification indicates that diphtheria toxin kills cells by inhibiting protein synthesis. The mechanism by which protein synthesis is inhibited by diphtheria toxin is by the ADP-ribosylation of elongation factor-2 (EF-2) which stops the translation of the

mRNA nucleotide sequence into a protein amino acid sequence at the ribosome of the cell (see specification, page 4, line 15 to page 5, line 2; and page 5, lines 13-18). However, the prior art teaches that EF-2 can be inhibited by means other than ADP-ribosylation, such as hyperphosphorylation (Johnson et al., the reference for which has been supplied by Applicant but is missing from Applicant's PTO-1449 filed 10/5/01, but which the Examiner has included on the PTO-892). In fact, Johnson et al. discloses that in the brains of AD patients, EF-2 is hyperphosphorylated (abstract, Figure 2, and pages 322-323). Applicant asserts that "the Johnson paper does not provide conclusive evidence that ADP-ribosylated EF-2 was associated with the altered migration and that such modification was not present in the brain samples" in two-dimensional gels (see specification, page 5, lines 7-9). The Examiner agrees with Applicant that the Johnson paper teaches that hyperphosphorylation and not ADP-ribosylation had occurred to the EF-2 on the gels and it was hyperphosphorylation and not ADP-ribosylation that produced the altered migrations in samples taken from the brains of AD patients. Therefore, the Johnson paper provides guidance, reasoning, and strong scientific evidence against the enablement of the instant invention because Johnson et al. provides a direct working example that the inhibition of protein synthesis in the brains of AD patients is caused by the hyperphosphorylation of EF-2 and not by ADP-ribosylation. There is no predictable reason taught by the instant specification as to why diphtheria toxin vaccine would have any effect at all on the hyperphosphorylation of EF-2 in brains of AD patients, and neither does any evidence exist in the prior art that the Examiner was able to find after searching.

In conclusion, for inventions drawn to the treatment of intractable and incurable (and hence, truly terrible) diseases such as AD, a significant burden of proof is placed on Applicant to provide either working examples, guidance, or sound scientific reasoning to support the enablement of said inventions. For all of the aforementioned reasons, the instant Application fails to provide adequate support to enable the instant claims.

Applicant's arguments entered 6/23/06 have been fully considered but they are not persuasive. Applicant argues that "the specification as a whole is concerned with any decline in immune surveillance, whether from a disease state...or perhaps even nutritional" (page 2 of Remarks). This is unpersuasive because the specification is silent in regards to nutrition and its relationship to declines in immune surveillance. Furthermore, because the immune system does not respond as well in aged populations as compared to younger populations (see page 3 of Remarks), then the prophetic invention, in the absence of any working examples or in vitro data or even an experimental model, must be supported with adequate guidance or scientific reasoning to enable the prophetic invention and place it into the hands of the public. Impaired immune function in the elderly runs counter to the enablement of the prophetic invention, absent any evidence to the contrary.

Applicant has stated that he does "not rely on the McLay reference for support" for enablement (Remarks, page 3), so the instant invention is bereft of any enabling support for its asserted operability.

Applicant also argues that the disclosure teaches that chronic (low-level) carrier states exist for C. diphtheria and P. Aeroginosa in the elderly that do not manifest in acute disease. The disclosure does not teach this in the manner as argued by Applicant. Instead, the specification teaches "there is a chronic carrier state for C. diphtheria, which reside in the nose and throat possibly as nonpathogenic organisms or weakened pathogenic organisms...(page 6, lines 16-19 of the specification, underlining mine). The specification provides no evidence to support this assertion which the Examiner does not accept at face-value because both the Applicant and Examiner agree that the immune systems of the elderly are somewhat impaired, so it is more likely than not that said pathogenic organisms would not be held in a nonpathogenic or weakened state by an elderly immune system.

Applicant argues that there is no basis for the assumption that younger AD patients are "non-immune impaired." In the absence of any showings of evidence, data, working examples, prior art citations, or general medical knowledge, there is a total lack of any basis for enablement that younger AD patients are immune impaired.

The guidelines for the control of diphtheria in Canada reference that Applicant's submitted with the after-final amendment indicated a total of 33 cases of clinical diphtheria in Canada over the 12-year period from 1986 to 1997. If there were so many asymptomatic "carriers" of diphtheria as the present disclosure appears to suggest, it would logically follow that epidemiologically there would be more clinical diphtheria cases presenting due to the decline of anti-diphtheria antibody titers that occur in individuals as time from last childhood vaccination increases, along with the decline of

immune function in old age. Additionally, those with impaired immune function from AIDS, chemotherapy for cancer, and immunosuppressive therapy for heterologous surgical transplants would also show an increased incidence for diphtheria, which does not appear to be the case with just 33 cases being reported over 12 years (less than 3 cases a year). If Applicant's hypothesis were correct, it would follow sound scientific reasoning that diphtheria incidence in the aged and these other populations would be somewhat increasing. Instead, Applicant is essentially arguing that the aged population is suffering from neuronal degeneration because of a carefully equilibrated epidemiological scenario where aged immunity declines not to the point where diphtheria incidence increases, but asymptomatic carriers are on the rise (but never ever leading to clinical diphtheria). Unfortunately, there is no evidence that such a precariously balanced immunological phenomenon is occurring, and the instant invention remains rejected for lack of enablement for reasons of record.

Finally, the inventor's own peer-reviewed and published work fails to support any enablement for the prophetic invention! Applicant asserts that "subtle amounts of ADP-ribosylation may well have occurred," but this is an unsupported assertion not backed up by any evidence or data. It is not enough to merely argue that the inventor's work does not absolutely rule out the operability of the invention; instead the standard for enablement is clearly dictated by USC 112, 1st paragraph:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such **full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the sam** and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Again, positive support must be provided for the instant invention (perhaps in the form of experimental evidence that would not be considered new matter, but would support the assertions of ADP-ribosylation over hyperphosphorylation as the experimental mechanism, as in a 1.132 declaration?), and not merely that the claimed invention lacks definitive negative experimental evidence that would indicate its inoperability.

3. No claim is allowed.

4. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technical Center 1600 general number which is (571) 272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (571) 272-0883. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached at (571) 272-0867. The fax phone number for this Group is currently (571)-273-8300.

SG

Stephen Gucker

August 3, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER